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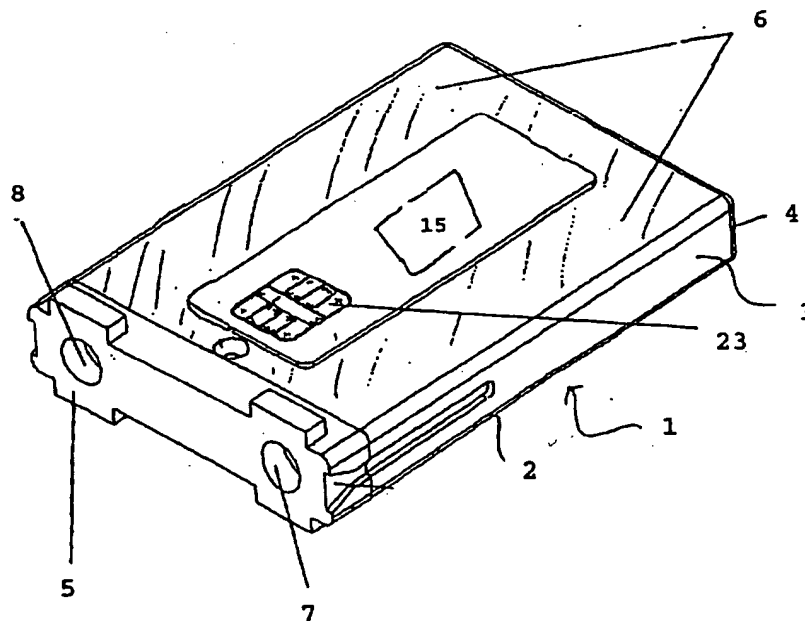
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(54) Title: FLUID SEPARATION CONDUIT CARTRIDGE



(57) Abstract: A fluid separation conduit cartridge comprising a fluid separation conduit is disclosed. In certain embodiments the fluid separation conduit is potted to provide operation at increased pressures. In other embodiments, the fluid separation conduit cartridge has one or more memory units. The memory units are operative to store data such as, for example, cartridge usage and test results.

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FLUID SEPARATION CONDUIT CARTRIDGE

5 Cross-Referenced Applications

This application claims priority to commonly assigned U.S. Patent Application No. 60/239,010 titled "Microfluidic Substrate Assembly and a Method for Making Same" and filed on October 06, 2000, commonly assigned U.S. Patent Application No. 60/239,063 titled "Liquid Separation Column Smart Cartridge " and filed on October 06, 2000, commonly assigned U.S. Patent Application No. 60/238,805 titled "Liquid Separation Column Smart Cartridge with Encryption Capability" and filed on October 06, 2000, and commonly assigned United States Patent Application No. 60/238,390 titled "Microfluidic Substrate Assembly and a Method for Making Same" and filed on October 06, 2000, the entire disclosure of each of which is hereby incorporated herein by reference for all purposes.

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Field of Invention

Embodiments of this invention are directed to a fluid separation conduit cartridge. More particularly, embodiments of this invention are directed to a fluid chromatography conduit cartridge comprising one or more memory units and/or connectors or potted conduits.

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Background

Molecules can be effectively separated by employing liquid chromatography ("LC"). A typical liquid chromatography system consists of a column and solvent that traverses the entire column. As the development of column packing material (also referred to as "stationary phase") progressed, high pressure was required to pump solvent through the column leading to the development of high pressure (or high performance) liquid chromatography (HPLC).

High performance liquid chromatography systems typically consist of high pressure pumps, at least one solvent reservoir, a column capable of withstanding relatively high pressures, and a detector. Columns used in HPLC typically consist of packing material. In most instances this packing material comprises silica-based particles typically with functional groups (defining a column's chemistry) attached to these silica-based particles. The packing of the column is a critical event in the construction of a specific column, for the integrity of the packed bed impacts

the overall resolution capability of the column. As the bed becomes disrupted through any series of events, for example, sharp periodic fluctuations in column pressure, resolution will decrease. Maintaining the integrity of the packing bed is essential if the original efficiency capability of a particular column is to be preserved. Through continued usage, the column's packed bed and the bonded phase deteriorate. The resolving power of the column is then lost. Detection and recordation of this loss of resolving power is very important.

Capillary liquid chromatography is a micro-version of traditional liquid chromatography. As is true for traditional liquid chromatography, the column used in capillary liquid chromatography is of critical importance. These columns typically have low solvent consumption and require low volumes of sample for analysis. These conditions translate into a higher degree of unit mass detectability. Capillary liquid chromatography systems typically comprise a micro-pumping unit, a capillary column, a detector, and a data processing system. Capillary liquid chromatography columns are typically produced using such materials as fused silica, stainless steel, or polymeric compositions. The lumen of the capillary is packed with packing material containing separation material, such as bonded silica particles. Typically, the internal diameter of the capillary column is between 50 and 500 μm .

Assessment of column quality is typically performed by running standard analytes through the column and comparing certain chromatographic parameters to a standard test run. Apart from performing a chromatographic run with known analytes, assessment of the column cannot be effectuated. Currently, columns themselves lack the ability to store their performance information which can be of great value. The performance record of a column is very important in environments where quality control is an issue, for example, in the pharmaceutical industry.

Summary

In accordance with a first aspect, a fluid separation conduit cartridge (also referred to below as a conduit cartridge) comprising at least a housing unit, a memory unit, and one or more connectors is disclosed. In preferred embodiments, the housing unit is manufactured from materials capable of withstanding high pressures and harsh environments. For example, the housing unit can be manufactured from steel, e.g. stainless steel or galvanized steel, such that rusting is minimized and strength is increased. In other embodiments, the housing unit is manufactured from plastics or polymers, such as polyetheretherketone (PEEK) for example, such

that the housing unit and components within the housing unit can be assembled rapidly, to minimize assembly costs, and to provide a lightweight device. The housing unit typically has one or more connectors, as described in detail below, to connect the conduit cartridge with an system, instrument or other device. The connectors are operative to create a fluid-tight seal
5 between the conduit cartridge and any device to which the conduit cartridge is interfaced, e.g. attached. As used here fluid refers to liquids and/or gases, e.g. supercritical fluids, etc., optionally containing particulate matter, dissolved species, solvated species, and the like. As used here, memory unit refers to any device that is operative to store, read, write, and/or read and write information. As used here information refers to any data, results, parameters, etc. used or
10 generated by an instrument or fluid separation conduit cartridge, e.g. manufacturing information, usage information, test results, and the like. Preferred memory units include but are not limited to memory chips, e.g., read only memory (ROMs), programmable read only memory (ROMs) erasable programmable read-only memory (EPROMs), electrically erasable programmable read-only memory (EEPROMs), DIMMs, SIMMs, and other memory units and memory chips well
15 known to those skilled in the art and commercially available from numerous manufacturers such as Siemens, Toshiba, Texas Instruments and Micron. In certain embodiments, the memory unit is integrally attached to the conduit cartridge, for example, at the time of its manufacture. In other embodiments, the memory unit may be removed and upgraded, for example, to a larger memory unit. In yet other embodiments, the memory unit is a component of a larger device or
20 circuit, e.g. a circuit comprising a microprocessor in electrical communication with the memory unit, for example. One skilled in the art given the benefit of this disclosure will be able to select suitable memory units for incorporation into the conduit cartridges disclosed here. The amount of information stored typically will depend upon the memory capacity, and how the information is recovered will depend on whether or not a microcontroller, e.g. a microprocessor, is
25 incorporated in the memory unit itself or is in electrical communication with the memory unit. Components could be read-only or read/write or be partitioned with a read-only area for manufacturing information and a read/write area for usage information. The information stored could vary from the minimal amount of data required to identify the cartridge and its quality control test performance in text format to a full quality control trace and usage history.

30 In accordance with another aspect, the fluid separation conduit cartridge may comprise a plurality of memory units. For example, a first memory unit may be specific for use on a

specific analytical system. This type of memory unit is customized for use with a specific manufacturer's analytical system e.g. a specific chromatography system. That is, the memory unit may be chosen such that it is compatible with or contains information such that the conduit cartridge is operative with a specific chromatography system, e.g. a Waters Alliance HPLC System or a Varian SD-2 Prep HPLC System, for example. The first memory unit may be readable and writeable. Preferably, the read-only area includes at least full conduit cartridge manufacturing and quality control test data. The writeable area can include at least a history of cartridge usage, number of injections, maximum used pressure, maximum used flow rate, pressure/flow profile, maximum temperature, serial number, cartridge parameters, e.g. number of theoretical plates, test results, or the like, as well as other features. A second memory unit is chosen such that the memory unit is operative with any analytical system. For example, the memory unit is a read-only memory unit and is supplied with a device to read the information in the memory unit and output the information in via, for example, a RS232 interface. The information may include but is not limited to cartridge manufacturing and quality control test data, conduit cartridge history, and the like.

In accordance with another aspect, the fluid separation conduit cartridge comprises a housing unit, a fluid separation conduit defined within the housing unit and a ferrule subassembly, as described above, at the housing inlet orifice and/or outlet orifice. The fluid separation conduit may be defined or formed, for example, by a lumen or tube, e.g., a flexible tube. Typically such tube is connected at one end to the inlet orifice and at the other end at the outlet orifice. The fluid separation conduit, or a portion thereof, may be defined by a channel formed from assembling individual layers into a multi-layer laminated substrate, such as the fluid handling substrates described in commonly assigned U.S. Patent Application No. 60/239,010 titled "Microfluidic Substrate Assembly and a Method of Making Same" and filed on October 06, 2000, the entire disclosure of which is hereby incorporated by reference for all purposes. In certain embodiments, the fluid separation conduit comprises one or more flexible tubes that terminate at opposite ends of a channel, e.g. a microfluidic channel, formed by assembling the layers of a multi-layer laminated substrate. That is, in certain embodiments the fluid separation conduit comprises at least one flexible tube in fluid communication with at least one channel, where the fluid separation conduit is defined by the at least one tube and the channel. The fluid separation conduit has at least first and second openings for entry and exit of fluid, respectively.

The cross-sectional diameter of the fluid separation conduit may vary depending on the desired flow rate, desired operation pressure, conduit shape, and the like. For example, for a cylindrical fluid separation conduit comprising a flexible tube, e.g. a coiled capillary tube, the inner diameter of the conduit can range from a few microns to about 4-5 mm. An exemplary inner diameter for a tubular conduit suitable to provide 1 uL/min flow rate under typical fluid pressures is about 320 um. Other exemplary inner diameters include about 50 um, about 75 um, about 800 um, about 1mm, about 2mm, and about 3.9 mm. An inner diameter of about 3.9 mm or 4.6 mm is suitable, for example, for certain conventional chromatography applications. Suitable wall thicknesses, e.g. the difference between an inner diameter and an outer diameter include, 1/16 of an inch, 1/4 of an inch, and 3/8 of an inch. In preferred embodiments, an inlet orifice in the housing unit is in fluid communication with a first end of the fluid separation conduit within the housing, and an outlet orifice in the housing unit is in fluid communication with a second end of the fluid separation conduit. The fluid separation conduit provides a fluid flow path within the housing from the inlet orifice to the outlet orifice. A first connector, e.g. a first ferrule-sub assembly, and a second connector, e.g. a second ferrule sub-assembly, can be fitted to the first end and the second end of the fluid separation conduit, respectively. More specifically, in embodiments comprising ferrule sub-assemblies each of the ferrule sub-assemblies comprises a ferrule or end cap seated over the end of the fluid separation conduit. The ferrule sub-assembly preferably comprises a compression ring securing the attachment to the fluid separation conduit and/or creating a fluid-tight seal between the end of the conduit and other channels or devices in fluid communication with the fluid separation conduit. The ferrule sub-assemblies, further described below, each preferably provides a seating and sealing surface for its respective fluid flow port. In preferred embodiments, the ferrule sub-assembly comprises a frit body providing the seating and sealing surface. Preferably each of the ferrule sub-assemblies is secured to the housing unit in a fixed position, optionally being removably fixed, at its respective port. In this manner, the fluid separation conduit can be conveniently anchored to the housing unit, e.g., to a component of the housing unit which is assembled with one or more other housing components after the fluid separation conduit is attached, to construct the housing unit of the conduit cartridge. In certain embodiments, a surface of the ferrule sub-assembly at the inlet end of the fluid separation conduit is a substantially flat surface having a fluid opening for the inlet port and facing substantially outwardly from the housing unit to seat and seal

conveniently against a corresponding surface of a fluid feed line or other fluid source feeding fluid to the fluid separation conduit cartridge for testing, analysis, etc. Similarly, a surface of the ferrule sub-assembly attached to the outlet end of the fluid separation conduit provides a substantially flat surface having a fluid opening for the outlet port and facing substantially outwardly from the housing to seat and seal conveniently against a corresponding surface of a fluid return or waste line or other fluid receiving device for accepting fluid from the fluid separation conduit cartridge after it has been tested, analyzed or subjected to other operation(s) by the fluid separation conduit within the housing. It should be recognized that the designation of a port of the housing unit as being an inlet port or an outlet port may in certain instances be arbitrary and merely a matter of convenience or choice, such as where the conduit cartridge is usable in either direction, preferably then being side-to-side symmetrical so that it can be properly installed in either orientation. In other embodiments, an outwardly extending connector is provided on a fluid separation conduit cartridge to enable insertion of the conduit cartridge fluid ports into wells or receiving sockets of a manifold or mounting device or the like, for fluid connection and sealing. As discussed above, the housing unit may comprise innumerable other devices positioned within or attached to the housing unit and or components thereof, e.g. the fluid separation conduit, the memory unit, the ferrule subassemblies, etc.

In accordance with an additional aspect, the fluid separation conduit cartridge disclosed here can be used to separate one or more species in a fluid. As used here, separate, separation, or fluid separation refers to resolving two or more species in the fluid. Preferably, baseline separation, e.g. baseline resolution, is achieved using the conduit cartridge disclosed here to provide for accurate quantitative measurements of the species in the fluid. The fluid separation conduit of the conduit cartridge disclosed here may take numerous forms, e.g. cylindrical, serpentine, coiled, and the like, and preferably contains one or more types of fluid separation media (also referred to below as a stationary phase(s)) for separating species in a fluid. As used here stationary phase refers to the material(s) coated, adsorbed, absorbed, or attached to the inner surfaces of the fluid separation conduit, e.g. the surfaces of the fluid separation conduit that are contacted by fluid from a fluid reservoir, for example. The stationary phase is operative to adsorb and to allow for desorption of species in the fluid, e.g. allows for reversible adsorption of species in the fluid. Based on the differential solubilities of the species in the fluid and in the stationary phase, the stationary phase acts to separate the species in the fluid. As used here

differential solubilities refers to the solubility of a species in the stationary phase and in a fluid passing over or through the stationary phase, e.g. the mobile or fluid phase. For example, if a given species is more soluble in the stationary phase than in the fluid phase, then the given species remains adsorbed to the fluid separation conduit and does not elute. However, when the species becomes more soluble in the fluid phase than in the stationary phase, e.g. by altering the composition of the fluid phase using a solvent gradient, for example, the species is desorbed from the stationary phase and elutes from the fluid separation conduit, e.g. flows out of the cartridge in the fluid phase. Because different species have different solubilities in the different phases, e.g. partition differently between the stationary and fluid phases, depending on the selected nature of the stationary phase and the fluids, separation of the species in a fluid can be achieved. The nature of the stationary phases may vary depending on the intended use of the fluid separation conduit cartridge. For example, C18 phases may be used for separation of generally non-polar species in a fluid while strong anion exchangers (SAX) might be used for separation of charged species in a fluid. One skilled in the art given the benefit of this disclosure will be able to select suitable stationary phases for an intended use. Preferably the stationary phase is selected from materials having nonpolar functional groups, e.g. C18 and the like, materials with negatively charged functional groups, e.g. $R_1\text{-SO}_3^-$ groups, $R_1\text{-COO}^-$ groups and the like, and materials with positively charged functional groups, e.g. $R_2\text{-NH}_3^+$ groups and the like, where R_1 and R_2 may be any group linked to the $\text{SO}_3^-/\text{COO}^-$ and NH_3^+ moieties respectively. Depending on the nature of the stationary phases, suitable fluid phases may be chosen such that the species in a fluid will elute at different times, e.g. the species will have different retention times. One skilled in the art given the benefit of this disclosure will be able to select suitable fluid phases for separating one or more species in a fluid. In preferred embodiments, a solvent gradient is used to separate the species in a fluid. As used here solvent gradient refers to changing the composition of the fluid phase with increasing time. Suitable solvent gradient methods will be apparent to those skilled in the art given the benefit of this disclosure and exemplary solvent gradient methods are discussed below.

In accordance with another aspect, the conduit cartridges typically are in fluid communication with one or more devices operative to move fluid into and/or out of the fluid separation conduit cartridge. That is, one or more devices, in fluid communication, with the conduit cartridges are operative to generate a fluid flow such that species introduced into the

fluid flow can enter into the conduit cartridge, be separated by the conduit cartridge, and/or subsequently flow out of the conduit cartridge. Suitable devices for generating a fluid flow are well known to those skilled in the art and include but are not limited to pumps, e.g. piston pumps, standard HPLC pumps and the like, vacuum manifolds, and the like. Those skilled in the art will recognize that these devices are useful in controlling the flow rate of species out of the conduit cartridge, e.g. are used to alter the retention times of the species, and thus can effect separation of the species. For example, lower fluid flow rates can be used to provide for better separation of the species, whereas higher fluid flow rates may be used to elute the species from the conduit cartridge more rapidly. One skilled in the art given the benefit of this disclosure will be able to select numerous devices for generating a fluid flow. Suitable devices may also be in fluid communication with one or more sample introduction devices, such as those described in detail below, e.g. fixed-loop injectors, auto-injectors, auto-samplers, and the like.

It will be recognized by those skilled in the art, given the benefit of this disclosure, that the fluid separation conduit cartridge disclosed above may include numerous other components. For example, additional columns, e.g. one or more guard columns, might be in fluid communication with the fluid separation conduit. Additional memory units, such as those discussed above, may be included in the conduit cartridge. Identifiers, such as RF tags, bar codes and the like may be placed on or in the housing unit of the cartridge. Additional connectors, e.g. electronic connectors such as, for example, PCMCIA connectors, serial connectors, parallel connectors, USB connectors and the like, may be positioned on any surface of the housing unit and optionally may be in electrical communication with one or more memory units. Such additional devices may be incorporated into the conduit cartridge in any of numerous manners, e.g. incorporated inside the housing unit of the conduit cartridge or may be removably attached to one or more outer surfaces of the housing unit. It will also be recognized by those skilled in the art, given the benefit of this disclosure, that the fluid separation conduit cartridges disclosed above may omit one or more of the components described above, e.g. a memory unit and/or a connector may be omitted. That is, in certain embodiments, the memory unit, for example, is omitted from the conduit cartridge disclosed above. Thus, in certain embodiments, the conduit cartridge may comprise a housing unit and one or more connectors but no memory unit. In other embodiments, the conduit cartridge may comprise a housing unit and a memory

unit but no connectors. One skilled in the art, given the benefit of this disclosure will be able to design conduit cartridges with selected components suitable for an intended use.

In accordance with additional aspects, a fluid separation conduit cartridge comprising at least a housing unit and a separation conduit that is potted is disclosed. As used here potted
5 refers to surrounding, e.g. enveloping, encasing, enclosing, and the like, one or more components of the cartridge with a potting compound. The potting compound prevents movement of the components within the conduit cartridge and provides protection to any sensitive components, e.g. a memory unit, within the cartridge. In certain embodiments, the potting compound envelops the conduit cartridge and allows the cartridge to withstand higher pressures without
10 rupturing, fracturing or leaking. Exemplary potting compounds include but are not limited to thermoset and thermoplastic polymers, e.g., epoxies, glass filled epoxies, metal filled epoxies, carbon-filled epoxies, and the like. In certain embodiments, the fluid separation conduit cartridge may comprise a housing unit, one or more memory units, one or more connectors, and a potted fluid separation conduit. The potting compounds typically have no effect on the
15 memory unit or any other components within the housing unit or attached to the housing unit. That is, the memory unit may be integrated into the housing unit of the cartridge and the potting compounds can be disposed in the housing unit to encapsulate the fluid separation conduit and the memory unit without adversely affecting operation of the conduit cartridge. The potting compound can be disposed prior to packing the conduit with a packing material or after packing
20 the conduit with a packing material. In certain embodiments, the conduit cartridge comprises a housing unit, one or more connectors, a potted conduit, and a memory unit. In yet other embodiments, the conduit cartridge comprises a housing unit, one or more connectors and a potted conduit but no memory unit. One skilled in the art, given the benefit of this disclosure, will be able to choose components for incorporation into the conduit cartridges disclosed here
25 suitable for an intended use.

In accordance with a method aspect, a method for making a fluid separation conduit cartridge comprising a fluid separation conduit and at least one memory unit is disclosed. An assembled cartridge is provided comprising all of the necessary elements for a fluid separation conduit including at least one memory unit. The fluid separation conduit and any other internal
30 components, e.g. the memory unit, may optionally be potted as discussed above. The memory unit can then be programmed at the manufacturing facility. The cartridge can then be loaded or

packed with a suitable packing material, e.g. a suitable stationary phase, based on the intended use of the fluid separation conduit cartridge. Numerous methods for loading stationary phases are well known to those skilled in the art and include, for example, flowing a slurry of a packing material into the conduit using a high pressure pump. Following the loading of the conduit with
5 a suitable stationary phase, the cartridge can undergo testing for quality assurance at the manufacturing facility the results of which may then be incorporated into the memory unit. Following use by an end-user, the cartridge can intermittently, e.g. daily, weekly, monthly, etc., throughout its lifetime be examined for quality control issues, for example, in the process of validation of a particular chromatographic method. The cartridge can be tested at a test site, for
10 example, within an end-user's facility, the results of which may be incorporated into the memory unit.

In accordance with an additional method aspect, a method for making a fluid separation conduit cartridge comprising a fluid separation conduit that is potted is disclosed. An assembled fluid separation conduit cartridge is provided, comprising at least a housing unit, and one or
15 more potting compounds are disposed within, or optionally on or around, the conduit cartridge. The potting compounds may be disposed using numerous methods known to those skilled in the art including but not limited to injection of the potting compound using a syringe and needle. In certain embodiments, one or more of the cartridge faces on the housing unit are removed, or not assembled, and the potting compound is poured or injected into the housing unit in a sufficient
20 amount to envelop at least a portion or all surfaces of the fluid separation conduit, more preferably enveloping substantially all surfaces, e.g. outer surfaces, of the fluid separation conduit that is located internally with the housing unit. In other embodiments, the potting compound is disposed in the conduit cartridge prior to, or simultaneously with, insertion of a fluid separation conduit into the housing unit. The cartridge can then be packed with a suitable
25 packing material, e.g. a suitable stationary phase, based on the intended use of the fluid separation conduit cartridge. Numerous methods for loading stationary phases are well known to those skilled in the art and include, for example, those mentioned above. Following the packing of the cartridge, the cartridge can undergo testing for quality assurance at the manufacturing facility, e.g. testing to assess cartridge quality and operation at high pressures.

30 Certain preferred embodiments of the fluid separation conduit cartridge disclosed here provide useful information as to the cartridge's performance that is critical in both Good

Manufacturing Practice and Good Laboratory Practice settings. Damaged conduit cartridges can be detected early, thereby saving on both frustration and useless data acquisition. Full traceability of the conduit cartridge throughout its lifetime is available to the end-user or any other interested party with appropriate access capabilities.

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Brief Description of the Figures

Certain preferred embodiments of the present invention will be described below with reference to the accompanying figures in which:

Fig. 1 is a perspective view of a fluid separation conduit cartridge, in accordance with preferred embodiments;

Fig. 2 is a cut-away view of the fluid separation conduit cartridge shown in Fig. 1, in accordance with preferred embodiments;

Fig. 3 is a block diagram of a circuit board contained within the housing of a fluid separation conduit cartridge, in accordance with preferred embodiments;

Fig. 4 is an exploded section view of a ferrule sub-assembly, in accordance with preferred embodiments;

Figs. 5a and 5b are schematic section views, partially broken away, showing the ferrule sub-assembly of Fig. 4 in use in cartridge, in accordance with preferred embodiments;

Figs. 6a and 6b are schematic section views, partially broken away, showing the fluid separation conduit of a conduit cartridge comprising ferrule sub-assemblies in accordance with the Fig. 4, being charged with fluid separation media, in accordance with preferred embodiments;

Fig. 7 is an exploded schematic view, partially broken away, showing a conduit cartridge comprising ferrule sub-assemblies in accordance with Fig. 4 mounted in fluid ports extending outwardly from an end cap or manifold of the housing unit of the conduit cartridge, in accordance with preferred embodiments;

Fig. 8 is a flow diagram of the method of producing a fluid separation conduit cartridge, in accordance with preferred embodiments;

Fig. 9 is a first embodiment of an analytical system in communication with a fluid separation conduit cartridge, in accordance with preferred embodiments;

Fig. 10 is an embodiment of a fluid separation conduit cartridge attached to a manifold of an analytical system, in accordance with preferred embodiments;

Fig. 11 is an embodiment of a fluid separation conduit cartridge attached to a manifold of an analytical system where the manifold is in fluid communication with a device for generating a fluid flow, in accordance with preferred embodiments; and

Fig. 12 is a second embodiment of an analytical system in communication with a fluid separation conduit cartridge, in accordance with preferred embodiments.

It will be recognized by those skilled in the art that the fluid separation conduit cartridges disclosed in Figs. 1-11 are not necessarily to scale. The dimensions of the cartridges may have been enlarged, relative to the dimensions of an analytical system or an instrument, for example, for ease of illustration and for clarity of viewing. Those skilled in the art given the benefit of this disclosure will recognize that the conduit cartridges may have any dimensions suitable for interfacing with any analytical system, for example.

Detailed Description of Certain Preferred Embodiments

It will be recognized by those skilled in the art that embodiments of the fluid separation conduit cartridge described here may be used for numerous fluid separation methods including but not limited to liquid chromatography (LC), high performance liquid chromatography (HPLC), fast performance liquid chromatography (FPLC), supercritical fluid (SCF) chromatography, gas chromatography (GC), capillary liquid chromatography, capillary electrophoresis, other liquid-phased separation techniques, e.g. micellar electrokinetic chromatography (MEKC), isoelectric focusing, isotachopheresis and other chromatographic methods commonly used by those skilled in the art. For convenience and not intending to limit the fluid separation conduit cartridge in any manner, the detailed description of certain preferred embodiments described here is directed to fluid separation conduit cartridges operative to be used in liquid chromatography. However, one skilled in the art, given the benefit of this disclosure will be able to design and use the fluid separation conduit cartridges disclosed here for these and other uses.

In accordance with certain preferred embodiments, a fluid separation conduit cartridge comprises an exterior portion and an interior portion. Referring to Fig. 1, the exterior portion is

defined by a housing unit 1 which comprises a base plate 2, at least two side plates 3, a rear manifold 4 which is perpendicular to the two side plates, a front manifold 5 that lies perpendicular to the two side plates, and a cover plate 6. An input orifice 7 and an output 8 orifice are shown. Both the input orifice 7 and output orifice 8 are disposed within the front manifold 5. The dimensions of the housing unit or its footprint, can vary depending on the intended use of the cartridge and upon the instrument or device to which the cartridge is intended to interface. For example, in certain embodiments the cartridge is about 1 $\frac{3}{4}$ inch, more typically about 3-4 inches wide by about 1 $\frac{3}{4}$ inches, more typically 4 $\frac{3}{4}$ to about 19 inches. The 19 inch dimension is a standard rack dimension and, accordingly, cartridges as disclosed here, in certain embodiments have one dimension equal to 19 inches or $\frac{1}{2}$ that size or other standard fraction of that full rack dimension. The thickness or height of the cartridge will follow somewhat the footprint dimensions and typically will be at least about $\frac{5}{8}$ of an inch or more. The cartridge, for example, may have the dimensions of a postage stamp, a PCMCIA card (especially a Type III PCMCIA card), a credit card, or the like. The thickness of the cartridge can also vary depending on the intended use of the cartridge. One skilled in the art given the benefit of this disclosure will be able to select suitable thicknesses and other dimensions for accommodating suitable components into the conduit cartridge and to provide the proper dimensions for interfacing the conduit cartridge with an instrument, analytical system, e.g. a chromatography system, or the like. Referring to Fig. 2, the input orifice 7 and output orifice 8 each comprise fittings (9, 10) that can be used to facilitate entry and exit, respectively, of a fluid, with or without any dissolved species or particulate matter, through the cartridge. The fittings 9, 10 can have an outer surface aspect and an inner surface aspect. The outer (or exterior) surface aspect interfaces with an exterior connection, such as an LC separation conduit 20 for example, carrying fluid. The inner (or interior) surface aspect interfaces with the interior of the housing unit 1. The fitting is secured within an orifice by numerous devices and methods known to those skilled in the art, e.g. clamps, adhesives, welding, and the like

In accordance with certain preferred embodiments and referring to Fig. 2, an LC separation conduit 20, housed within the interior of the housing unit 1, with two defined ends is attached at a first end 21 to input orifice fitting 9 and is attached at a second end 22 to output orifice fitting 10. Numerous methods suitable for attachment are well known to those skilled in the art and include, for example, snap-connectors, solvent welding, IR welding, compression

5 fittings, adhesives and the like. Preferably, input orifice fitting 9 and output orifice fitting 10 each is coated with a substance in order to maintain a fluid-tight seal. That is, each fitting is preferably coated with a material that assists in preventing any fluid from permeating between the junction formed by an orifice fitting and surface of the manifold. Examples of such materials include but are not limited to polytetrafluorethylene, e.g. TeflonTM tape and TeflonTM coatings (e.g. sprayed on TeflonTM coating), and other polymer materials such as polyethylene, PEEK coatings, PCTFE (e.g. KEL-FTM), and the like.. In preferred embodiments, a capillary conduit, e.g. a capillary column, is used in the conduit cartridge. The capillary column comprises a tube having a lumen with a first end and a second end. The capillary column can be manufactured from numerous materials including but not limited to fused silica, glass, polyetheretherketone (or PEEK), as well as other polymeric materials well known in the art. In certain embodiments, additives, such as carbon black, dyes, titanium dioxide, gold, e.g. electroplated gold or electrolessly plated gold, carbon particles, additional polymers, e.g. a secondary polymer or second phase polymer reactive with the primary polymer of the laminate layer, IR absorbing materials, and the like, may be included, as a surface coating and/or a body filler, in the materials used to form the column. The first end of the capillary column can interface with the inner surface aspect of the input orifice fitting (that is, the surface aspect which is interior within the housing unit), while the second end can interface with the inner surface aspect of the exit orifice fitting. The length of the capillary column in the present embodiment can range from about 6 cm to about 25 cm though longer capillary columns may be used by coiling the column within the housing unit. The rear manifold 4 and front manifold 5 can be positioned and secured into place with the remaining housing unit 1 by methods and devices well known to those skilled in the art. Suitable methods and devices for securing the manifolds to the housing unit include but are not limited to employing an adhesive agent, a screw forming a male unit which is then placed in apposition with a female union, a preformed male connector placed in apposition with a female union, and the like.

30 In accordance with certain preferred embodiments, the conduit cartridges disclosed here are typically in fluid communication with one or more devices operative to generate a fluid flow. The fluid typically comprises a buffer or solvent and any dissolved analytes or species, as discussed above. In preferred embodiments, a plurality of devices for generating a fluid flow are used such that solvent gradients may be implemented to achieve better, and more efficient,

separations between the species in the fluid. The choice of devices typically depends on the amount of solvent to be moved within a period. That is, the choice of devices for generating a fluid flow typically depends on the desired flow rate necessary to achieve separation of the species. For example, in preferred embodiments, one or more pumps are in fluid communication with the conduit cartridge, and optionally with one or more injectors, e.g. fixed-loop injectors, auto-injectors, auto-samplers, and the like, for introducing samples into the fluid flow. Suitable pumps include but are not limited micro-pumps, which typically can generate a fluid flow rate between about 30 $\mu\text{L}/\text{min}$ and about 100 $\mu\text{L}/\text{min}$, analytical pumps, which typically can generate a fluid flow rate between about 1 $\mu\text{L}/\text{min}$ to about 10 mL/min , semi-preparative pumps, which typically can generate a fluid flow rate up to about 20 mL/min , and preparative pumps, which typically can generate a fluid flow rate up to about 50 mL/min . Numerous other pumps are commercially available from manufacturers such as Waters, Inc. and Jasco, Inc. When switched on, the pumps draw fluid from solvent or buffer reservoirs and force fluid through the remainder of the fluid circuit, e.g. force fluid into the conduit cartridge. Any species in the fluid can be separated using the conduit cartridge, as discussed above. Depending on the solvent(s) chosen for the method, the species elute, e.g. exit the conduit cartridge, based on their differential solubilities in the fluid phase and the stationary phase. As discussed above, it is preferred that solvent gradients are used to facilitate rapid separation of the species. As used here, solvent gradient refers to varying the composition of the fluid phase with time. That is, during the separation run, e.g. the method, the composition of the fluid phase is altered such that at specified intervals during the separation run, the composition of the solvent is altered. For example, if initially, e.g. when the sample is introduced into the conduit cartridge, the fluid phase comprises 80% solvent A and 20% solvent B, then during the separation run, the composition of the fluid phase may be altered such that at a specified interval, e.g. 5 minutes after the starting the separation run, the composition of the fluid phase is 60% A and 40% B. Such alterations can be achieved in a linear fashion, a step-wise fashion, or other commonly used parameters for generating and designing solvent gradients known to those skilled in the art. One skilled in the art given the benefit of this disclosure will be able to select suitable devices for generating a fluid flow and suitable solvents and flow rate for achieving separation of species in a fluid sample.

In accordance with certain preferred embodiments, the external portion, and/or the internal portion as the case may be, of the cartridge may comprise at least one electrical

connector (not shown). That is, an electrical connector may be positioned on any external and/or internal surface of the housing unit of the cartridge. Preferably, the front manifold comprises an electrical connector. Suitable electrical connectors include power and communication connectors, e.g. AC or DC power connectors, electrical leads, PCMCIA connectors, PCI
5 connectors, serial connectors, parallel connectors, USB connectors, firewire connectors, optical and fiber-optical connectors, coaxial connectors, BCN connectors, SCSI connectors, ribbon connectors, RS-232 interfaces, and the like. One skilled in the art given the benefit of this disclosure will be able to select electrical connectors suitable for operation of the conduit cartridges disclosed here. The conduit cartridges may also include numerous other connectors,
10 e.g. fluid connectors, as discussed in detail below.

In accordance with certain preferred embodiments, a fluid separation conduit cartridge comprises a housing unit and at least one memory unit. The memory unit of the conduit cartridges disclosed here is suitable for use in embodiments comprising the potted conduit and also in embodiments where the conduit is not potted. That is, the memory unit may be
15 incorporated into conduit cartridges where the conduit is potted, e.g. either inside the housing unit or outside the housing unit, and the memory unit itself may be potted without adversely affecting operation of the memory unit. For example, referring to Fig. 3, the conduit cartridge may comprise at least one read-write memory unit 30. Examples of different types of suitable memory units are well known to those skilled in the art, e.g. a Dallas Semiconductor chip
20 DS1994 4K-Bit Plus Time Touch Memory. Suitable memory units typically include at least an Input/Output portion 32 along with memory 34 and optionally may include a processor 36, e.g. a microprocessor.

In accordance with certain preferred embodiments, the conduit cartridge preferably comprises at least two types of memory units. A first memory unit is chosen such that it is
25 compatible with a specific analytical system. That is, the first memory unit is chosen such that is designed to interface with a specific manufacturer's analytical system, e.g. commercially available HPLC systems and the like. Preferably, the first memory unit is readable and writeable. The read-only area may include, for example, full cartridge manufacturing, quality control test data, and any other data and parameters deemed necessary by the manufacturer. The
30 writeable area can comprise a history of cartridge usage, for example, number of injections, maximum used pressure, maximum used flow rate, pressure/flow profile, maximum temperature,

as well as other features. When the conduit cartridge comprising a memory unit is placed in a particular analytical system, e.g. a chromatography instrument, the conduit cartridge details are read into the analytical system and the analytical system sets-up according to the method contained within the memory unit of the conduit cartridge. This feature allows for non-expert operators to perform an analysis without having detailed knowledge of information required to program the analytical system. On completion of the analysis, the cartridge's usage information, for example, flow rate, pressure, analysis method, number of injections, last calibration run date and reference, last used date and the like, can be updated and encoded into the memory unit. A second memory unit is chosen such that it is operative in any analytical system. The second memory unit preferably is a read-only memory unit and is supplied with a device to read the memory unit and output information in via, for example, a PCMCIA interface. The information in the second memory unit can include cartridge manufacturing, quality control test data, and other data or information relevant to the manufacturing and testing of the conduit cartridge. In general, the types of information that can be stored into the memory units include all parameters that describe the cartridge geometry and construction; also, all parameters that describe any packings, coatings or accessory chemistries, such as, filters and guard columns. Time stamp information can also be encoded into the memory unit. This information can be stored at the time the cartridge is manufactured. Additional information that can be stored is related to, for example, the method to be employed by the fluid separation conduit cartridge. Each fluid separation conduit cartridge typically is designed for a given application and dedicated to that use for the life of a particular conduit cartridge. Other information that can be stored on the memory units includes standard overall separation parameters, such as run time, data acquisition, and sampling rate. Also, the names and expected retention times and retention time windows for any targets and/or expected analytes which will be eluted from the cartridge during the separation run can be stored in the memory unit. One skilled in the art given the benefit of this disclosure will be able to select information for storing in the memory units of the conduit cartridges disclosed here.

In accordance with certain preferred embodiments, throughout the lifetime of the fluid separation conduit cartridge, quality control information can be stored in the memory unit to provide for continuous validation of the conduit cartridge, e.g. to provide quality control measures to ensure that the conduit cartridge is operating properly. For example, the number of

injections, maximum used pressure, maximum used flow rate, pressure/flow profile, maximum temperature, etc., can be stored within the memory unit. This information can be later accessed by a test center or at the manufacturing facility. Performance status can also be measured by subsequent testing of the cartridge's ability to facilitate separation of test analytes. The results
5 can be compared to the test analysis performed at the manufacturing facility prior to delivery of the fluid separation conduit cartridge to an end-user. This capability allows for lifetime validation of the cartridge. Potentially the cartridge may be passed along to several end-users, however, the data stored within the memory unit will remain with the conduit cartridge.

In accordance with certain preferred embodiments, as disclosed above, ferrule assemblies
10 can be employed as fittings on the ends of the fluid separation conduit cartridge. The ferrule assemblies are received into correspondingly sized sockets in the housing unit, preferably with a friction fit or, alternatively, with a snap-fit, with adhesive or other materials or devices to form a permanent or removably fixed connection between the ferrule and the housing unit. The ferrule fittings in this way serve to anchor the ends of the fluid separation conduit to the housing unit of
15 the conduit cartridge. Preferably, the ferrule fittings are received into an end plate of the housing unit, with the two ends of the fluid separation conduit extending back through the end plate into the interior of the housing unit formed by an open-ended concave housing member attached to, and closed by, the end plate. The ferrule assemblies advantageously provide an externally facing seating and sealing surface for fluid flow into or out of the fluid separation conduit. Preferably,
20 the ferrule is in the form of a cap, preferably being formed of metal or other suitable material. An annular wall extending from an end wall of the ferrule forms a socket into which the end of the fluid separation conduit is inserted. Preferably the ferrule socket forms a tight fit with the fluid separation conduit. A compression ring seats around the exterior of the annular wall. The compression ring, as its name suggests, is sized to compress the ferrule socket on the end of the
25 conduit to secure it in position. Preferably the end of the annular wall is beveled or chamfered to ease its insertion into the compression ring. The compression ring typically has a somewhat conical inside wall, larger toward the end wall of ferrule, such that its fit around the annular wall of the ferrule gets tighter as it is forced on. The ferrule has a fluid flow passage extending through the end wall, whereby fluid can flow to or from the fluid separation conduit through the
30 end wall. The ferrule sub-assembly further comprises a frit body at the exterior surface of the end wall to provide a seating and sealing surface. The frit body is seated in a well in the exterior

face of the ferrule over the end of the fluid flow passage, optionally standing slightly proud of the exterior face of the ferrule, to serve as a seating and sealing surface. In use, a fluid delivery line or fluid removal line mated to the conduit cartridge to establish delivery and removal of fluid to be tested by the conduit cartridge, can be pressed against the frit body to establish a fluid-tight seal with a sufficient degree of give or resiliency to accommodate manufacturing tolerances, dissimilar temperature expansion coefficients and the like.

In accordance with certain preferred embodiments, the materials used to construct the ferrule assemblies, conduits, and other connectors of the conduit cartridge may be altered and/or reinforced to withstand high pressures depending on the intended use of the conduit cartridge. For example, stainless steels and other metal plates can be used to reinforce the housing unit of the conduit cartridge. In certain embodiments, a multi-laminate structure can be included to provide increased strength for withstanding high pressures achieved using high flow rates, e.g. pressures greater than or equal to about 200 psi or 300 psi, for example up to about 2000 psi or more. One skilled in the art given the benefit of this disclosure will be able to select suitable materials for forming the connectors of the conduit cartridge disclosed here including but not limited to stainless steel, PEEK, reinforced PEEK, brass, ceramics, ceramic composites, etc.. Other suitable materials will be readily apparent to those skilled in the art given the benefit of this disclosure.

In accordance with certain preferred embodiments, referring now to Fig. 4, a ferrule sub-assembly 102 shown in exploded view is seen to comprise a ferrule 104 having an end wall 106 with an exterior surface 108 and an annular wall 110 forming a ferrule socket to receive a first end 112 of a fluid separation conduit 116. While the drawings are not necessarily to scale, inside surface 114 of annular wall 110 is sized to form a friction fit, or other tight fit, with the exterior surface of the first end 112 of the fluid separation conduit 116. Compression ring 118, preferably being formed of stainless steel or other suitable material, has a slightly conical inside surface 120. The beveled end 122 of annular wall 110 eases insertion of the annular wall into the compression ring. Fitting the compression ring onto annular wall 110 tightens the fit around the fluid separation conduit. Frit body 124 is seated in well 126 in the exterior surface 108 of end wall 106 of the ferrule 104. The frit body stands slightly proud of the exterior surface 108, that is, it extends beyond exterior wall 108 slightly. Referring now to Figs. 5a and 5b, a ferrule sub-assembly 102 as described above is seated on fluid separation conduit 116 that extends through

end plate 130 of a housing unit of a conduit cartridge. It can be seen that socket 132 in end wall 130 will receive ferrule sub-assembly 102. Typically, the assembled structure shown in Fig. 5a is pressed into socket 132 using any suitable mechanical device, e.g. mechanical press, and/or pulled in by the fluid separation conduit. The result is shown in Fig. 5b, wherein the ferrule sub-assembly is seated in socket 132 and fluid separation conduit 116 extends rearwardly into the housing unit of the conduit cartridge. While, for simplicity of illustration, the second end of fluid separation conduit 116 is not shown, it will be readily understood by those skilled in the art that a ferrule sub-assembly similar to or the same as sub-assembly 102 described above can be fitted to the second end of the fluid separation conduit and seated in socket 134 of the end wall 130 of the housing unit.

In accordance with certain preferred embodiments, the components disclosed above, e.g. the connectors and memory units, may be incorporated into conduit cartridges where the conduit is potted. That is, a fluid separation conduit cartridge may comprise a potted conduit, one or more memory units, and one or more connectors. The fluid separation conduit cartridges may also comprise a display unit, such as a liquid crystal display unit 15 shown in Fig. 1, inserted within or atop an outer surface of the housing unit, such as the cover plate 6. This display unit 15 may be connected to a memory unit located within the housing unit 1. The display unit can display information stored in the memory unit, such that certain information, e.g. date of cartridge packing, may be discovered without interfacing the conduit cartridge to an instrument or other device. Any number of numerous other components may also be included in the conduit cartridges disclosed here.

In accordance with certain preferred embodiments, Fig. 7 shows an additional embodiment of a fluid separation conduit cartridge. A housing unit of a conduit cartridge comprises an endplate 204 secured at interface 206 to an open-ended concave housing component 202. A fluid separation conduit (not shown) is located within the housing component 202. The first end of the fluid separation conduit terminates at a ferrule sub-assembly 212, as described above. The second end of the fluid separation conduit terminates at ferrule sub-assembly 214. Thus, ferrule sub-assembly 212 forms an inlet orifice and ferrule sub-assembly 214 forms an outlet orifice for the conduit cartridge. The inlet orifice is located in an outwardly extending projection 208 of the endplate 204. The fluid separation conduit extends rearwardly (or upwardly as shown in Fig. 7) through the endplate 204 into the housing chamber formed by

housing component 202. Similarly, the outlet orifice formed by ferrule sub-assembly 214 is located in an outwardly extending projection 210 of the endplate 204, and the second end of the fluid separation conduit passes through endplate 204 to ferrule sub-assembly 214 at the outward end of projection 210. The first outwardly extending projection 208 and the second outwardly extending projection 210 each is substantially frusto-conical and symmetrical about the axis of the inlet and outlet orifices, respectively. Preferably the housing unit is generally planar, having its smallest dimension into the plane of the paper as viewed in Fig. 7. The outwardly extending projections preferably are substantially symmetrical and parallel projecting generally in the plane of the housing unit. One skilled in the art given the benefit of this disclosure will be able to use these and other suitable connectors for connecting the conduit cartridges disclosed here to suitable devices, such as analytical instruments, for example.

In accordance with certain preferred embodiments, a method for the construction of a fluid separation conduit cartridge comprising a memory unit is shown in Fig. 8. An assembled conduit cartridge 300 capable of performing chromatography, for example, is provided, which may comprise a potted conduit and/or a memory unit as described herein before. In embodiments comprising a memory unit, the conduit cartridge is programmed 302 or personalized, at the manufacturing site, for an intended use. That is, methods, parameters, information, data and the like are programmed into the conduit cartridge prior to shipping the conduit cartridge to the end user. In embodiments comprising a potted compound but no memory unit, this step may be omitted. The type of information written into the memory unit when it is personalized for a particular user method includes but is not limited to method parameters defining a liquid chromatographic (LC) or capillary electrophoretic (CE) or other liquid-phase separation, such as micellar electrokinetic chromatography (MEKC or MECC) separation to be employed by the particular fluid separation conduit cartridge. Other information can include but is not limited to data acquisition parameters, solvent gradient control parameters, expected target molecule names, IUPAC identifiers and retention time windows, detector response factors, other operational and analytical parameters used by commercial chromatographic data stations, the date and time of cartridge personalization and any other information desirable to or requested by an end-user. Subsequently, test performance (also known as method validation) data would typically be stored to the memory unit with the time and date obtained. The memory unit is capable of storing acquired data in its memory with an

indicator of cartridge usage. Examples of different types of read/writeable memory units are discussed above and other memory units are well known to those skilled in the art. It should be appreciated that information stored onto the memory unit can be encrypted, as discussed in the commonly assigned patent applications which have been incorporated by reference for all purposes. Additional information may be coded onto the conduit cartridge in the form of a bar code, a magnetic strip, or semiconductor chip. The device employed to read the code from the fluid separation conduit cartridge will depend on the format and medium of the code contained within the memory unit, examples of which include but are not limited to bar code readers, magnetic strip readers, a radio transponder, an inductive loop, ultrasonic, infrared, direct connection, an optical detector, electrical impulse detector or a data bus socket, all of the aforementioned methods and devices being well known to those skilled in the art.

In accordance with certain preferred embodiments, the conduit cartridge is loaded or packed 304 with a suitable packing material, e.g. a stationary phase, for the intended use of the conduit cartridge. As discussed above, the chemistry, e.g. functional groups, of the stationary phase typically depends on the intended use and the nature of the species in the fluid to be separated. One skilled in the art given the benefit of this disclosure will be able to select suitable stationary phases for separating species in fluids introduced into the conduit cartridges disclosed here. The assembled and packed fluid separation conduit cartridge can be validated 306, e.g. tested, at the manufacturing site to determine if the cartridge complies with known specifications pertinent to a particular chromatographic method. For example, known analytes specific for a particular chemistry can be subjected to chromatographic separation using the newly formed fluid separation conduit cartridge and suitable fluid mobile phases. Resolution, along with other chromatographic parameters, can be determined based upon the performance of the cartridge with a given set of known analytes. This process is a similar operation to that performed when validating a chromatographic method. The information obtained from this testing can then be stored in the memory unit. This test information can subsequently be used as a benchmark for determining the performance status of the cartridge once the apparatus has left the manufacturing facility and is in the hands of an end user. If the cartridge meets approval, then the apparatus as a whole can be certified in digital format stored in the memory unit by the manufacturer.

In accordance with certain preferred embodiments, after validating the cartridge, the result of the validation process can be written 308 to the cartridge. Additionally, the specific

chemistry of the packing material and any separation methods can be written into the memory unit of the conduit cartridge. For example, if the packing material comprises cationic functional groups, then a separation for anion exchange can be written to the memory unit.

In accordance with certain preferred embodiments, a method for construction of a fluid separation conduit cartridge comprising a fluid separation conduit that is potted is disclosed. The method comprises providing an assembled conduit cartridge and disposing at least one potting compound in the housing of the conduit cartridge. The potting compound may be disposed using numerous methods known to those skilled in the art including but not limited to injecting the compound using tubing, a syringe, and the like, pouring the compound into the housing using a vessel containing the potting compound, etc. In certain embodiments, the potting compound is disposed in the housing unit prior to insertion of the fluid separation conduit. After the potting compound is disposed around the fluid separation conduit, packing material, e.g. a stationary phase, is introduced into the fluid separation conduit. The specific chemistry of the packing material typically depends on the intended use of the cartridge and the species in the fluid that are to be separated. Numerous methods for packing the stationary phase are known to those skilled in the art and including those discussed above, and the like. Other methods will be readily apparent to those skilled in the art given the benefit of this disclosure. For example, Fig. 6a shows an embodiment for packing of a stationary phase into the fluid separation conduit. A device 140, preferably a needle with a syringe or tubing, is connected to the open end of a fluid separation conduit 22. The first end of the fluid separation conduit is fitted with a ferrule sub-assembly as described above, and is already seated in socket 132 of the manifold or end plate 130 of the housing unit of the conduit cartridge. After loading the packing material, an additional ferrule sub-assembly is added to the second end of the fluid separation conduit 22 (see Fig. 6b). The second end of the conduit is then pressed into socket 134 of the housing unit using manual or mechanical force or pressure, for example. Subsequent to packing the conduit, quality assurance tests may be performed on the cartridge to ensure that the cartridge will perform properly at the end user's facility. Numerous other steps may be performed after testing the cartridge, e.g. storage solvents may be introduced, the cartridge may be cleaned, etc.

Several examples of a fluid separation conduit cartridge are described below. The examples are not intended to limit the fluid separation conduit cartridges described here in any manner.

Example 1

An example of a fluid separation conduit cartridge interfaced with an analytical system, e.g. a chromatography system, is shown in Fig. 9. The analytical system typically is positioned within an end-user's facility for automated analyses. That is, the analytical system may be positioned near, or in-line, e.g. within the sample flow itself, such that analysis of samples may occur automatically, e.g. using auto-samplers, auto-injectors, and the like, or to facilitate rapid analysis of samples, e.g. samples during a process by an operator at an end-user's facility. For example, the system can be configured for analysis at specified intervals, e.g. every minute, hour, day, etc., such that continuous monitoring of a process can be performed with little or no user input. That is, the system can be configured to run a chromatographic method at a specified time interval without additional input from an operator. Referring to Fig. 9, the analytical system 400 typically comprises a conduit cartridge 410 interfaced with an analytical system, e.g. a chromatography instrument. Numerous mechanisms for interfacing the conduit cartridge with the analytical system are known to those skilled in the art and exemplary interfaces are described below. The analytical system optionally comprises a treatment unit 402, such as a filter, a guard column, a solid phase extraction silo for analyte pre-concentration, etc. The analytes may be pre-concentrated such that trace levels of analyte are concentrated to levels that are detectable by the analytical system. That is, the concentration of an analyte may be increased 10^1 , 10^2 , 10^3 , 10^4 , 10^5 , 10^6 , 10^7 , 10^8 , 10^9 times or higher to levels that are easily detected using the detector of the analytical system. The treatment units are optional and may be replaced with other chromatographic devices, such as, for example, guard columns, filters, semi-permeable membranes, etc. Alternatively, the treatment units can be replaced with a fluid flow channel such that little or no operations are performed on the fluid prior to entry into the conduit cartridge.

The system also typically includes a graphical user interface 404 for programming the system, e.g. the method, and/or monitoring system performance. The graphical interface may take numerous forms such as, for example, a keypad, an LCD screen, a touch screen, e.g. a touch screen display unit, etc. In certain embodiments, the graphical user interface is omitted and the information on the conduit cartridge is used to program the system. The system optionally contains a receiver/transmitter 406 to provide for remote operation and diagnosis, e.g. operation

of the analytical system over the Internet and/or transmission of data over the Internet to a remote facility. In certain embodiments, the conduit cartridge itself comprises a receiver/transmitter, and thus the receiver/transmitter of the analytical system may be omitted.

The system typically includes at least one detector 408. The type of detector used typically depends on the optical and physical properties of the species in the fluid. Preferred embodiments of the detector include at least a flow cell, e.g. a flow cell detector in communication with the cartridge. Additionally, the detectors are usually interchangeable such that the detector may be switched to a different type of detector, e.g. from a UV-Visible absorbance detector to a fluorescence detector. Suitable detectors include but are not limited to UV-Visible absorbance detectors, IR detectors, fluorescence detectors, electrochemical detectors, voltammetric detectors, coulometric detectors, potentiometric detectors, thermal detectors, ionization detectors, NMR detectors, EPR detectors, Raman detectors, refractive index detectors, ultrasonic detectors, photothermal detectors, photoacoustic detectors, evaporative light scattering detectors, mass-spectrometric detectors, and the like. The conduit cartridge 410 typically interfaces with the system through a manifold, which is discussed in detail below. In alternative embodiments, however, the conduit cartridge can interface directly with the system, e.g. can be connected directly to a fluid supply source, e.g. a pump and/or injector, without any intervening mechanical components, for example.

A closeable face plate 415 may be hingeably or removably attached to the system and can be closed over, or around, the system to protect the system from harsh environmental conditions, such as chemical solvents, UV radiation and the like. Supplying power and data to the chromatography system is a power and communication interface 416. Such interfaces typically are operative to provide a power source to the system, and can also provide communication of the system to a central computer, e.g. a computer in communication with the system for monitoring test results and/or for receiving information from the system.

To achieve high reproducibility, a fixed-loop injector 414 is typically used to introduce sample into the system. Suitable fixed-loop injectors are well known to those skilled in the art and are commercially available from numerous sources, e.g. Beckman Instruments (Fullerton, CA). Other injectors may be used in place of the fixed-loop injector depending on the intended use of the system. For example, auto-injectors and/or auto-samplers may be used to provide for automated sampling and analysis of fluids. Suitable auto-samplers and auto-injectors are well

known to those skilled in the art and are commercially available from numerous manufacturers. Optionally, the system can be programmed such that the auto-samplers and/or auto-injectors take samples at specified intervals, e.g. every 10 seconds, every minute, hourly, daily, weekly, monthly, etc., such that testing of the fluid can be performed without any input from a user. The
5 system also includes precise microfluidics for accurate solvent gradients and includes solvent reservoirs and/or reagent magazines 418 for providing a fluid phase for running the chromatographic methods of the conduit cartridge, e.g. solvent gradients and the like. Such precise microfluidics can be achieved using numerous methods known to those skilled in the art, such as the methods described in the commonly assigned U.S. Patent Applications incorporated
10 herein by reference for all purposes. As discussed above, typically in fluid communication with the solvent reservoirs are one or more pumps, which are operative to generate a fluid flow.

Typically the system installation can be customized such that the system can be positioned in numerous places in a facility. That is, the dimensions and shapes of the system can be designed for placement of the system in numerous areas of an operating facility, and the
15 functions, e.g. the chromatographic methods, of the system can be tailored to perform innumerable tests desired by an end-user. In preferred embodiments, the system is placed near the sample or process to be monitored. That is, the system may be placed, either fixably or removably mounted, for example, near the fluid to be analyzed. For example, the system can be custom mounted to a conduit 420 that carries a fluid sample, e.g. river water, out of a
20 manufacturing facility, for example. Depending upon the configuration of the system, the system can automatically sample the fluid flowing through the conduit, e.g. using an auto-sampler, auto-injector and the like, or one or more valves positioned in the conduit can be connected to the analytical system for introducing samples into the system. Alternatively, an operator can manually take samples from the conduit and can introduce the samples through a
25 fixed-loop injector, for example, using a needle, syringe, and the like. One skilled in the art given the benefit of this disclosure will be able to select suitable positions for the system described here depending on the type of analyses to be performed by the system

The fluid separation conduit cartridge typically interfaces with an analytical system through a manifold, e.g. the multi-layer laminated manifold 456 shown in Fig. 10. In Fig. 10, the
30 conduit cartridge 452 will be understood to be analogous to conduit cartridge 410 shown in Fig. 9. The manifold 456 is seen in the particular embodiment of Fig. 10 to be a multi-layer

laminated structure and has one or more microfluidic channels for introducing fluid into or receiving fluid from the fluid separation conduit cartridge. For example, the manifold 456 may comprise a first layer 458 attached to a second layer 459 which itself is attached to a third layer 460. As can be seen in Fig. 10, the second layer 459 typically is sandwiched between the first layer 458 and the third layer 460. Fluid channels can be provided within and/or at the interface(s) of the layers of such manifolds. For example, layer 459 in the manifold 456 of Fig. 10 can optionally be constructed as a microfluidic substrate assembly described in commonly assigned U.S. Patent Application No. 60/239,010 titled "Microfluidic Substrate Assembly and a Method of Making Same" and filed on October 06, 2000, the entire disclosure of which is hereby incorporated herein by reference for all purposes. The layers of the multi-layer laminated manifold each can be manufactured from any of numerous materials, including but not limited to PEEK, steel, e.g. stainless steel, and the like. Different layers of the multi-layer laminated manifold may be formed of different materials. In certain embodiments, the microfluidic flow channel is between two or more of the layers, e.g. the microfluidic flow channel can extend from the third layer into the second layer and optionally into the first layer, for example. The microfluidic flow channel can be formed in one or more of the layers using numerous techniques, e.g. UV embossing, micro-machining, micro-milling, and the like. For example, a micro-channel can be etched into the second layer and the first layer such that when the second layer is assembled to the first layer a fluid-tight microfluidic flow channel is created. As discussed above, the layers can be assembled to form the multi-layer laminated manifold. For example, the layers can be assembled by welding the layers together, optionally with a gasket positioned between the layers, or can be assembled using adhesives and the like. One skilled in the art given the benefit of this disclosure will be able to select suitable methods for assembling the layers of multi-layer laminated manifolds suitable for use with the conduit cartridges disclosed here. Preferably, the manifold comprises at least a first microfluidic channel in fluid communication with a solvent reservoir and with the input orifice of the fluid separation conduit cartridge. Thus solvent may flow into the conduit cartridge through a microfluidic channel in the manifold, e.g. by pumping the fluid into the cartridge using a pump. The manifold can include a second microfluidic channel that is in fluid communication with an output orifice of the conduit cartridge and typically is also in fluid communication with a detector. Therefore, a sample may be introduced into the conduit cartridge through the first microfluidic channel in the manifold,

separated by the conduit cartridge, and the separated species can flow out of the conduit cartridge through the second microfluidic channel in the manifold to a detector that can measure the amount and nature of the species present in the sample. One skilled in the art given the benefit of this disclosure will be able to design other suitable manifolds and devices for interfacing the
5 conduit cartridge with an analytical system.

The manifold may also contain an interface 454 mounted to the manifold. The interface typically is operative to create a fluid-tight seal when the cartridge is plugged into the manifold. That is, interface 454 is operative to provide a sealing force suitable to prevent fluid from leaking between the manifold and the fluid separation conduit cartridge. Optionally, one or more gaskets
10 can be positioned between the conduit cartridge and the interface to aid in forming a fluid-tight seal. One skilled in the art, given the benefit of this disclosure, will be able to select suitable interfaces and mechanisms for retaining the conduit cartridge against the manifold to create a fluid-tight seal. Exemplary mechanisms include cams, springs, pressure plates, welding, clamps, gear drives, , and combinations of any of them, adapted to be actuated by gravity or manually, by
15 solenoid, pneumatically, hydraulically, etc. As discussed above, in alternative embodiments the conduit cartridge is plugged directly into the system without using a manifold. For example, suitable connectors may be added to the conduit cartridge such that the conduit cartridge can be in direct fluid communication with a flow line, e.g. a flow line including one or more solvents and one or more species to be separated. One skilled in the art given the benefit of this
20 disclosure will be able to select suitable mechanisms and devices for interfacing the conduit cartridge disclosed here to a chromatography system.

In other embodiments, the manifold itself is in communication with a device for generating a fluid flow. For example, referring to Fig. 11, a pump 470 can be attached to the manifold and can be configured such that fluid is drawn from a fluid reservoir, e.g a solvent
25 reservoir, and is forced into the manifold and subsequently into conduit cartridge 452. Such devices may be any of the devices discussed above including but not limited to pumps, vacuum manifolds and the like. The device for generating a fluid flow can also be in communication with one or more injectors and discussed above.

Example 2

An additional example of a fluid separation conduit cartridge interfaced with an analytical system is shown in Fig. 12. The analytical system 500 comprises a fluid separation conduit cartridge 502, e.g. a cartridge operative to perform capillary liquid chromatography, a graphical user interface 504, and buffer cassettes 506. The graphical user interface can be used to program the system and/or the fluid separation conduit cartridge for a specific method, e.g. a specific solvent gradient, run time, flow rate, and the like. As discussed above, the graphical user interface can be omitted in embodiments where the conduit cartridge is operative to program the system, e.g. where the conduit cartridge comprises an analytical method in a memory unit, for example. The buffer cassettes are equivalent to solvent reservoirs. That is, the buffer cassettes may be loaded with any suitable mobile phase needed to perform a chromatographic method, for example. Preferably, the mobile phases are different in different buffer cassettes such that solvent gradients can be implemented in the analytical method. The buffer cassettes may be in communication with one or more devices that are operative to generate a fluid flow (not shown), e.g. pumps and the like. The system 500 typically has one or more power and communication interfaces 508 and can be custom installed 512 at a user's facility such that automated analyses may take place or such that the system is positioned near the fluid to be analyzed. As discussed above, the communication interface may send and/or receive data to or from a central computer, or other device. The system can be controlled by remote operation and diagnosis using a communication device 510 by various methods, such as for example, e-mail over the Internet. The communication device typically is used to alter the method of the system without having to manually enter the new method using the graphical user interface. This feature provides for remote configuration, or reconfiguration as the case may be, of the system. In certain embodiments, the communication device is omitted and the system is controlled by information sent from the conduit cartridge to the system. As can be seen in Fig. 12, the size of the fluid separation conduit cartridge can be tailored such that it has the appropriate dimensions, e.g. height, width and thickness, and has the appropriate connectors to interface with any analytical system. For example, in embodiments comprising a capillary column, the dimensions of the conduit cartridge may be reduced such that the footprint of the cartridge is smaller and occupies less space on the analytical system. Suitable fluid connectors including those discussed here, e.g. ferrule subassemblies and the like, can be attached to the conduit cartridges and are

typically operative to create a fluid-tight seal between the conduit cartridge and the analytical system. Suitable electrical connectors can be attached to the conduit cartridge including those discussed above, for example, PCMCIA connectors, USB connectors, serial connectors and the like. The electrical connectors typically provide for transfer of information to and from the
5 conduit cartridge.

As discussed above, the fluid separation conduit cartridge can interface with the system through a manifold, such as the manifold shown in Fig. 10, or can interface with the system directly, e.g. without any intervening physical components. Suitable connectors for interfacing with the manifold can be positioned on any surface of the housing unit of the conduit cartridge.

10 The fluid separation conduit cartridge 502 may include one or more connectors on a major surface, e.g. the back surface of the conduit cartridge 502 shown in Fig. 12, such that the conduit cartridge can interface with a manifold and sit flush with the surface of the system. For example, the conduit cartridge may have outwardly projecting connectors that plug into a manifold, having receiving socket, positioned on the analytical system. When the conduit cartridge is plugged into
15 the manifold, the conduit cartridge snaps into position on the analytical system, e.g. becomes seated in a slot on the surface of the analytical system. Thus, the conduit cartridge is in fluid communication with the analytical system and is retained by the system such that vibrations will not dislodge the conduit cartridge from the system, i.e. the conduit cartridge remains in fluid communication with the system even in the presence of vibrations or other physical disturbances.

20 Numerous other devices, e.g. cams, pulleys, springs, pressure plates and the like may be used to retain the conduit cartridge against the manifold of the system such that a fluid tight seal is preserved.

Although the present invention has been described above in terms of specific embodiments, it is anticipated that other uses, alterations and modifications thereof will become
25 apparent to those skilled in the art given the benefit of this disclosure. It is intended that the following claims be read as covering such alterations and modifications as fall within the true spirit and scope of the invention. It is intended that the articles "a" and "an", as used below in the claims, cover both the singular and plural forms of the nouns which the articles modify.

What is claimed is:

1. A fluid separation conduit cartridge comprising:
 - a housing unit;
 - 5 a fluid separation conduit within the housing unit;
 - an inlet orifice in fluid communication with a first end of the fluid separation conduit;
 - an outlet orifice in fluid communication with a second end of the fluid separation conduit, the fluid separation conduit providing a fluid flow path within the housing unit from the inlet orifice to the outlet orifice, wherein at least one of the inlet orifice and the outlet orifice comprises a ferrule sub-assembly, seated in the inlet orifice or the outlet orifice, comprising a ferrule defining a ferrule socket receiving one end of the fluid separation conduit, a ferrule ring on the ferrule, and a frit body at an exterior surface of the ferrule; and
 - 10 the ferrule; and
 - 15 a memory unit mounted to the housing unit.
2. The fluid separation conduit cartridge in accordance with claim 1, in which the fluid separation conduit is potted.
- 20 3. The fluid separation conduit cartridge in accordance with claim 1, in which the fluid separation conduit is a flexible tube.
4. The fluid separation conduit cartridge in accordance with claim 1, in which the fluid separation conduit is a microfluidic channel defined by a multi-layer laminated substrate.
- 25 5. The fluid separation conduit cartridge in accordance with claim 1, in which the inlet orifice is in a first projection extending outwardly from the housing unit and the outlet orifice is in a second projection extending outwardly from the housing unit.
- 30 6. The fluid separation conduit cartridge in accordance with claim 5, in which the housing unit comprises an end plate secured to and closing an open-ended concave housing components,

and the first projection and the second projection are substantially symmetrical and parallel projections from the end plate of the housing unit.

7. The fluid separation conduit cartridge in accordance with claim 1, in which the fluid
5 separation conduit comprises a packing material.

8. The fluid separation conduit cartridge in accordance with claim 7, in which the packing
material is operative to separate species in a fluid that are introduced into the fluid separation
conduit.

10

9. The fluid separation conduit cartridge in accordance with claim 7, in which the packing
material is selected from the group consisting of materials with nonpolar functional groups,
materials with negatively charged functional groups, and materials with positively charged
functional groups.

15

10. A fluid separation conduit cartridge comprising:
a housing unit;
a fluid separation conduit within the housing unit;
an inlet orifice in fluid communication with a first end of the fluid separation
20 conduit; and
an outlet orifice in fluid communication with a second end of the fluid separation
conduit, the fluid separation conduit providing a fluid flow path within the housing unit
from the inlet orifice to the outlet orifice, wherein at least one of the inlet orifice and the
outlet orifice comprises a ferrule sub-assembly, seated in the inlet orifice or the outlet
25 orifice, comprising a ferrule defining a ferrule socket receiving one end of the fluid
separation conduit, a ferrule ring on the ferrule, and a frit body at an exterior surface of
the ferrule.

25

11. The fluid separation conduit cartridge in accordance with claim 10, in which the fluid
30 separation conduit is potted.

12. The fluid separation conduit cartridge in accordance with claim 10, in which the ferrule has a fluid flow passage extending through an end wall of the ferrule to the ferrule socket.
13. The fluid separation conduit cartridge in accordance with claim 12, in which the frit
5 body is positioned at an exterior surface of the end wall.
14. The fluid separation conduit cartridge in accordance with claim 12, in which the frit body is seated in a well in the exterior face of the end wall.
- 10 15. The fluid separation conduit cartridge in accordance with claim 12, in which the frit body stands proud of the exterior face of the ferrule and is operative to serve as a seating and sealing surface.
16. A fluid separation conduit cartridge comprising:
- 15 a housing unit;
 a fluid separation conduit within the housing unit;
 a potting compound potting the fluid separation conduit in the housing unit;
 an inlet orifice in fluid communication with a first end of the fluid separation
 conduit; and
20 an outlet orifice in fluid communication with a second end of the fluid separation
 conduit, the fluid separation conduit providing a fluid flow path within the housing unit
 from the inlet orifice to the outlet orifice.
17. The fluid separation conduit cartridge in accordance with claim 16, in which the potting
25 compound is selected from the group consisting of epoxies, glass filled epoxies, metal filled epoxies, and carbon-filled epoxies.
18. The fluid separation conduit cartridge in accordance with claim 16, further comprising a
memory unit.

30

19. The fluid separation conduit cartridge in accordance with claim 16, further comprising a packing material in the fluid separation conduit, the packing material being operative to separate species in a fluid that are introduced into the fluid separation conduit.

5 20. A method of making a fluid separation conduit cartridge, the method comprising:
providing a housing unit including at least a first orifice;
inserting a fluid separation conduit in the at least first orifice of the housing unit;
attaching a first end of the fluid separation conduit to an inlet port in the housing
unit; and
10 attaching a second end of the fluid separation conduit to an outlet port in the
housing unit.

21. The method of claim 20, further comprising packing a stationary phase in the fluid
separation conduit.

15

22. The method of claim 20, further comprising disposing a potting compound in the housing
unit in a manner to surround the fluid separation conduit.

23. An analytical system comprising:
20 a fluid flow channel;
a fluid separation conduit cartridge; and
a detector, the fluid separation conduit cartridge being in fluid communication with
the fluid flow channel and comprising
a housing unit,
25 a fluid separation conduit within the housing unit,
an inlet orifice in fluid communication with a first end of the fluid
separation conduit,
an outlet orifice in fluid communication with a second end of the
fluid separation conduit and in fluid communication with the detector, the
30 fluid separation conduit providing a fluid flow path within the housing
unit from the inlet orifice to the outlet orifice, wherein at least one of the

inlet orifice and the outlet orifice comprises a ferrule sub-assembly, seated in the inlet orifice or the outlet orifice, comprising a ferrule defining a ferrule socket receiving one end of the fluid separation conduit, a ferrule ring on the ferrule, and a frit body at an exterior surface of the ferrule, and
5 a memory unit mounted to the housing unit.

24. The analytical system of claim 23, further comprising a device for generating fluid flow to the inlet orifice.

10 25. The analytical system of claim 24, in which the device for generating fluid flow is a pump.

26. The analytical system of claim 23, further comprising a treatment unit in fluid communication with the fluid flow channel and the fluid separation conduit cartridge, the
15 treatment unit being positioned between the fluid flow channel and the inlet orifice of the fluid separation conduit cartridge.

27. The analytical system of claim 26, in which the treatment unit is a guard column, a filters, or at least one pre-concentrations silo.

20

28. The analytical system of claim 23, wherein the fluid flow channel is defined within a multi-layer laminated manifold.

25

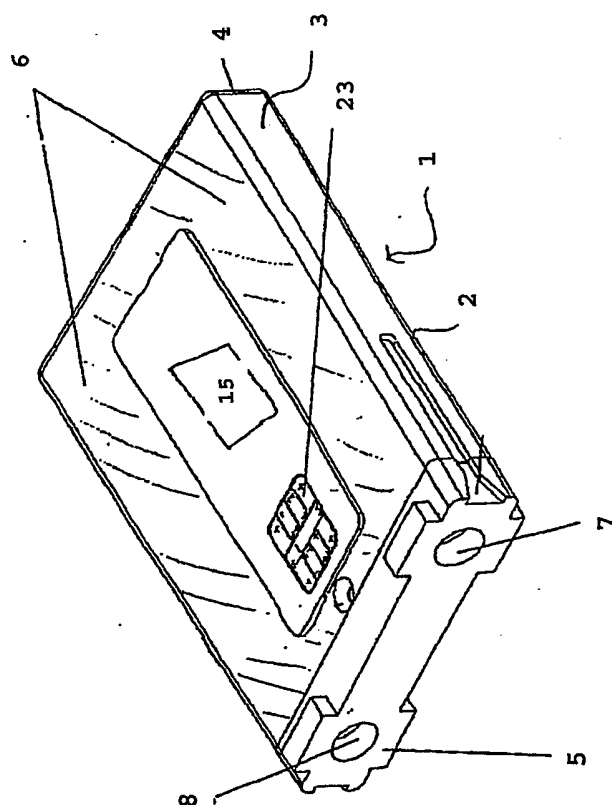


Fig. 1

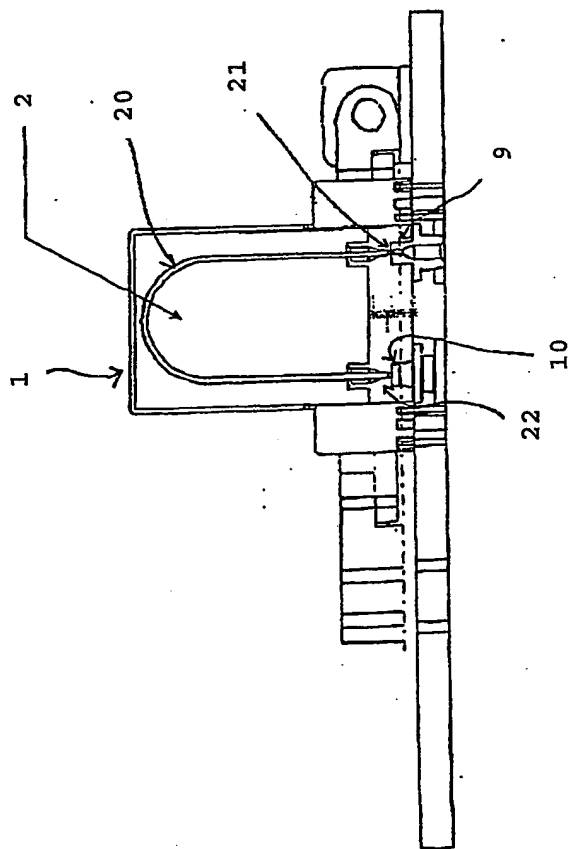


Fig. 2

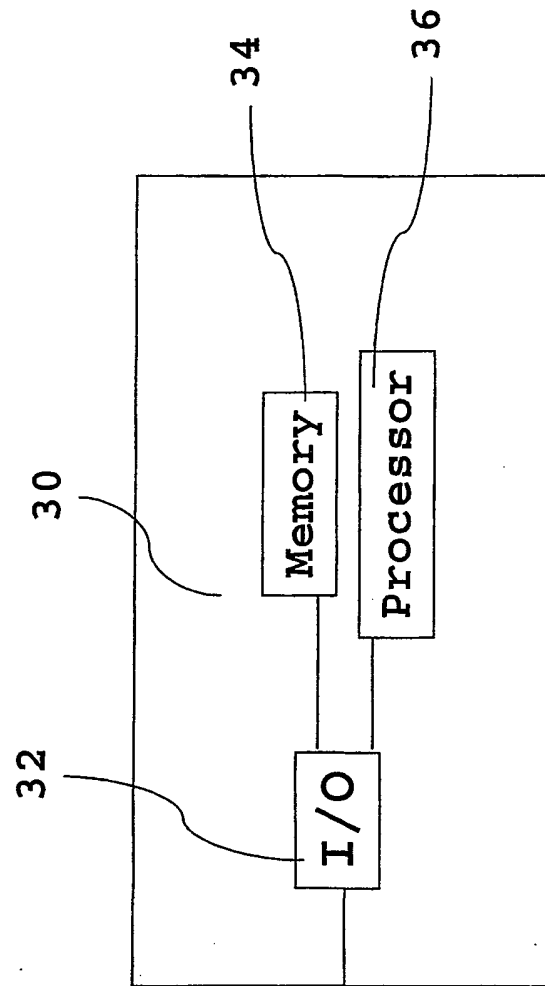


Fig. 3

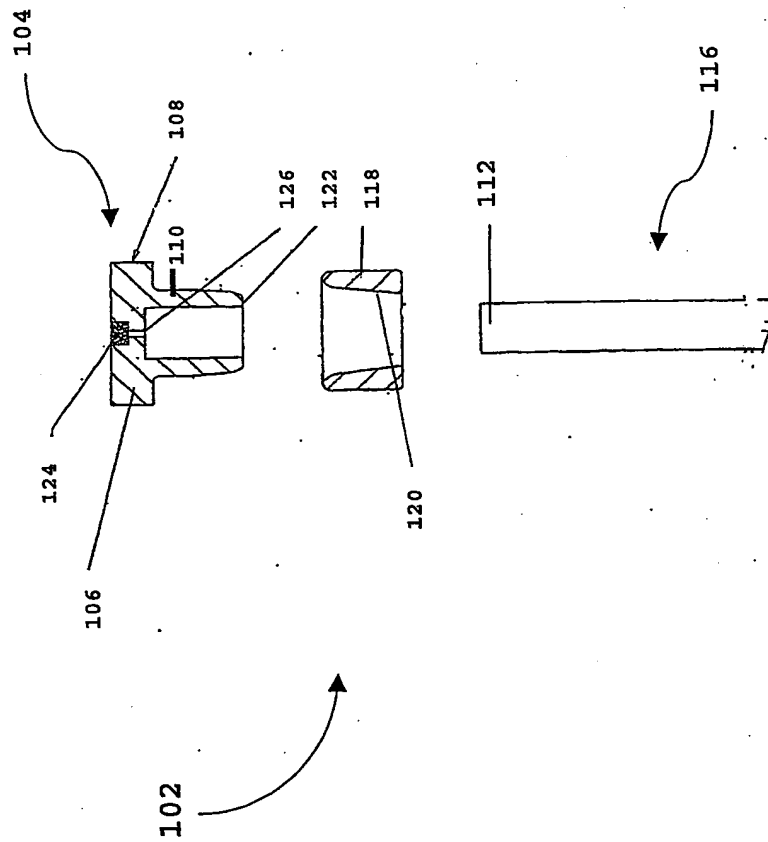


Fig. 4

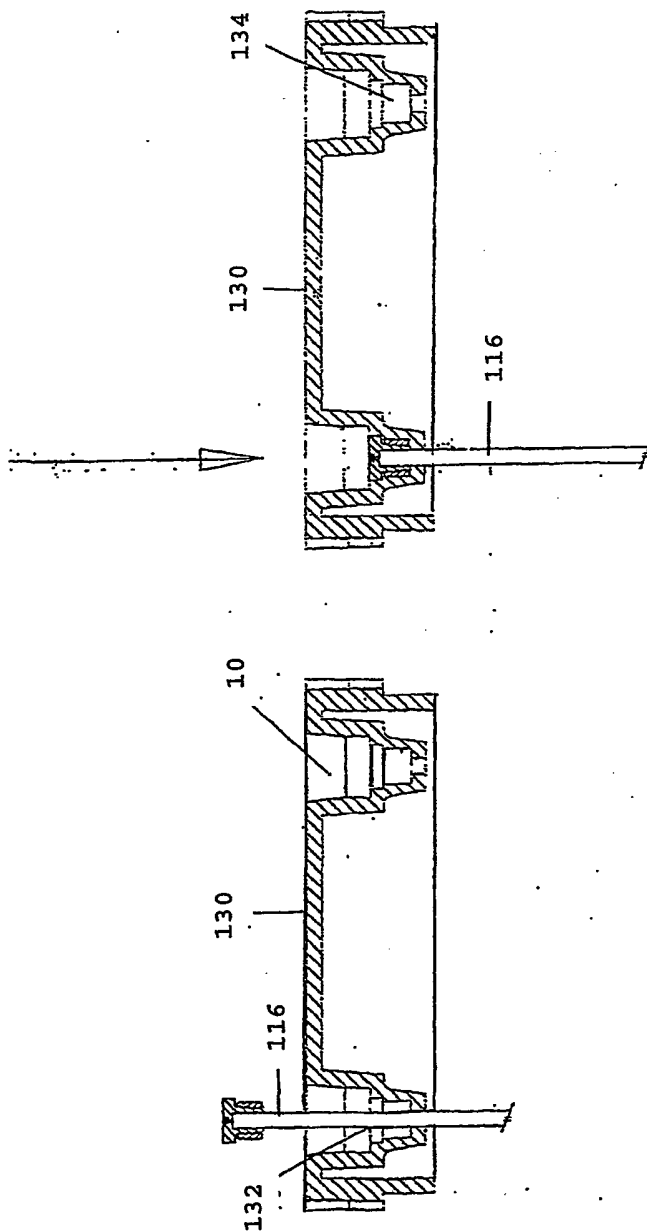


Fig. 5b

Fig. 5a

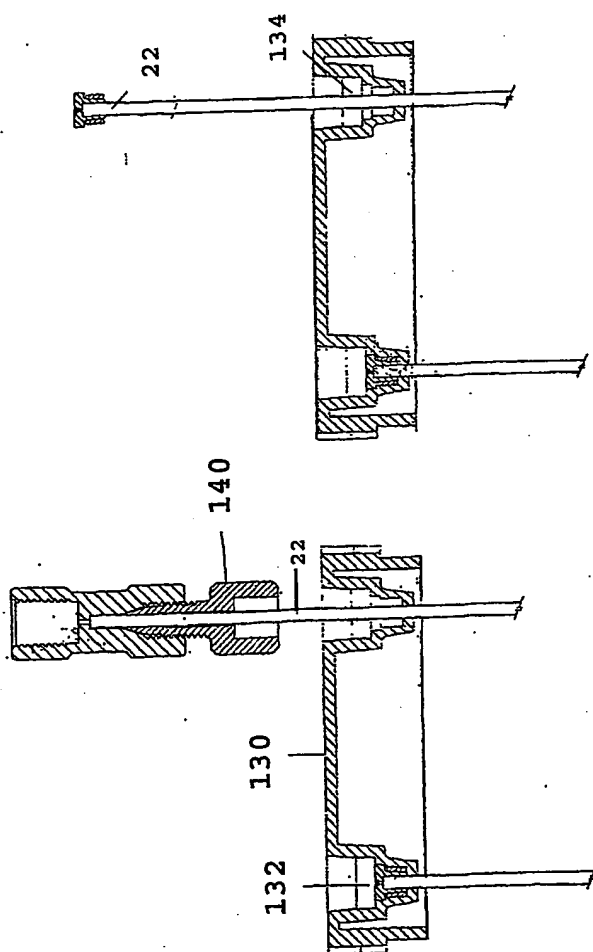


Fig. 6b

Fig. 6a

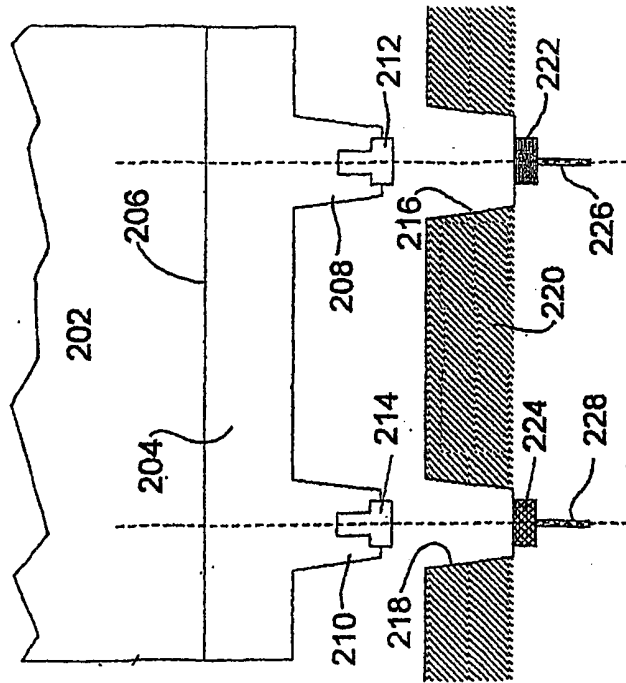


Fig. 7

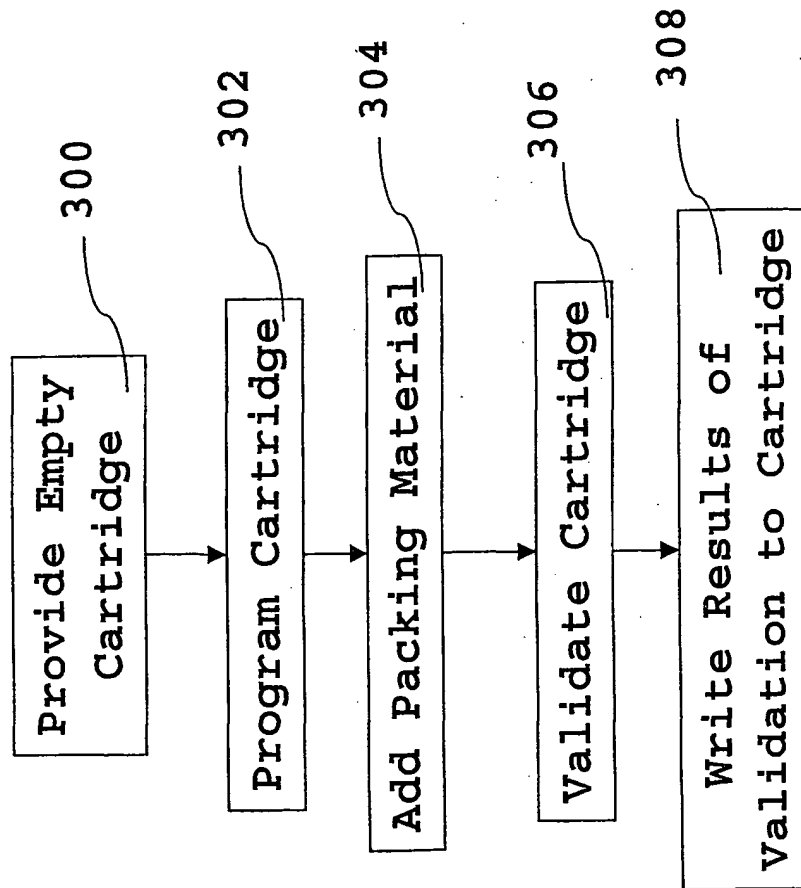


Fig. 8

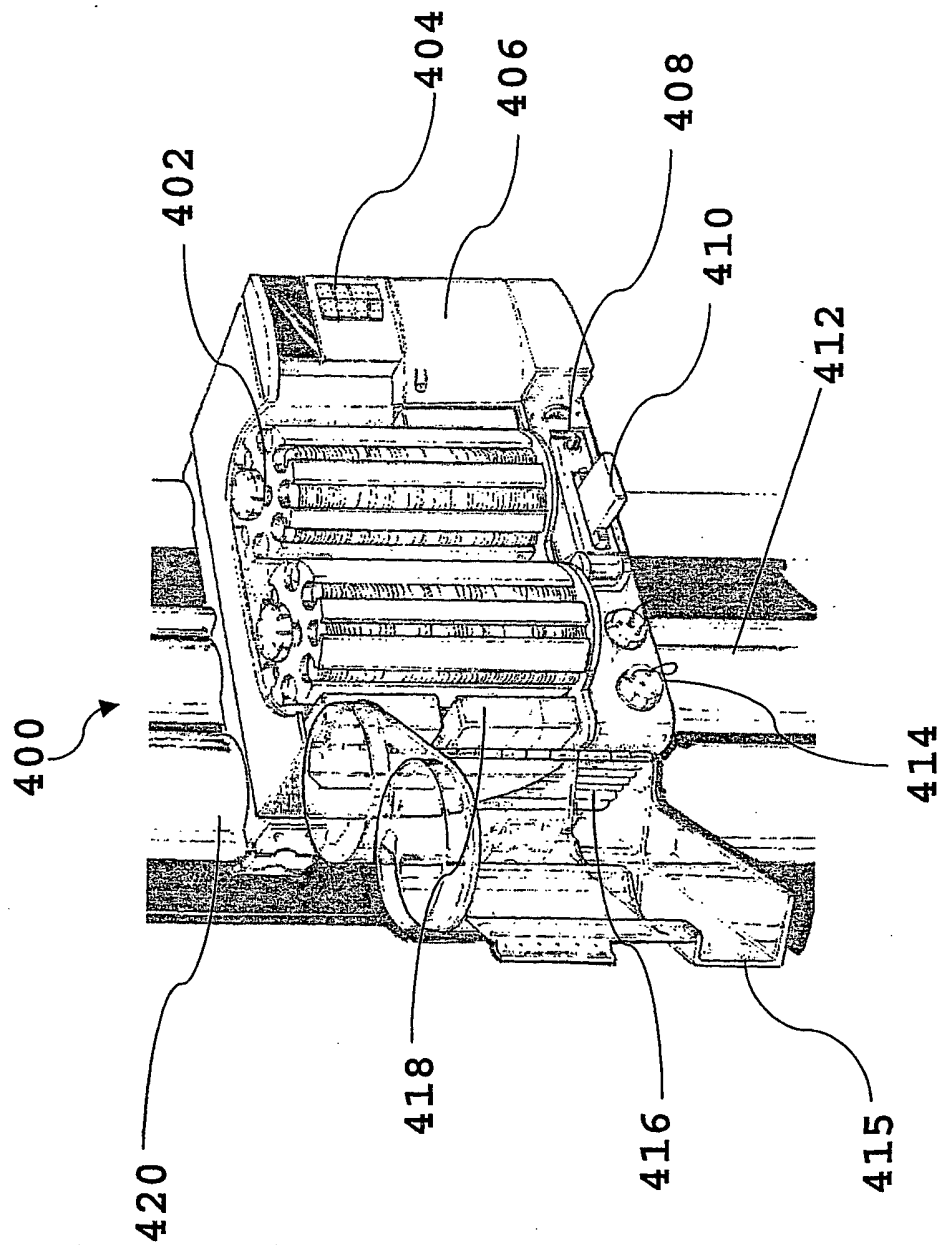
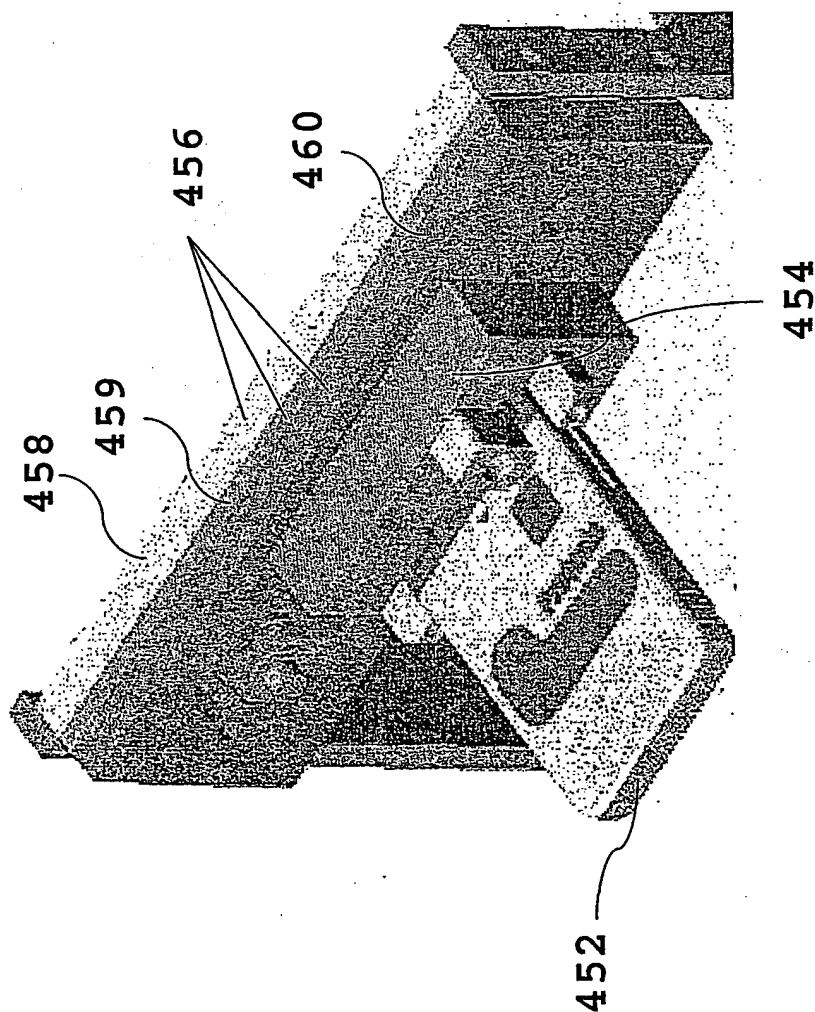


Fig. 9



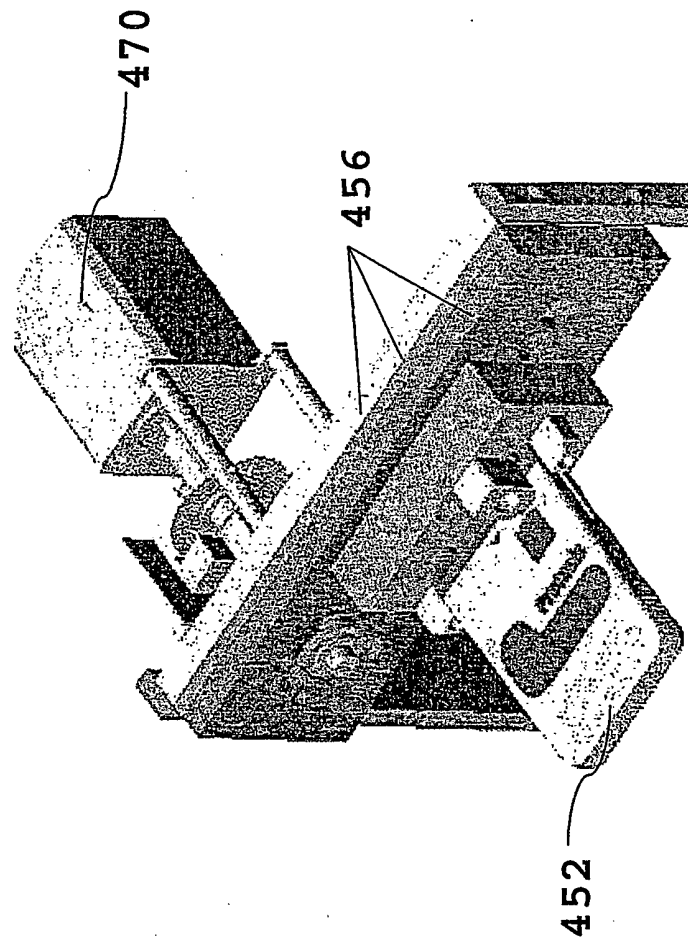


Fig. 11

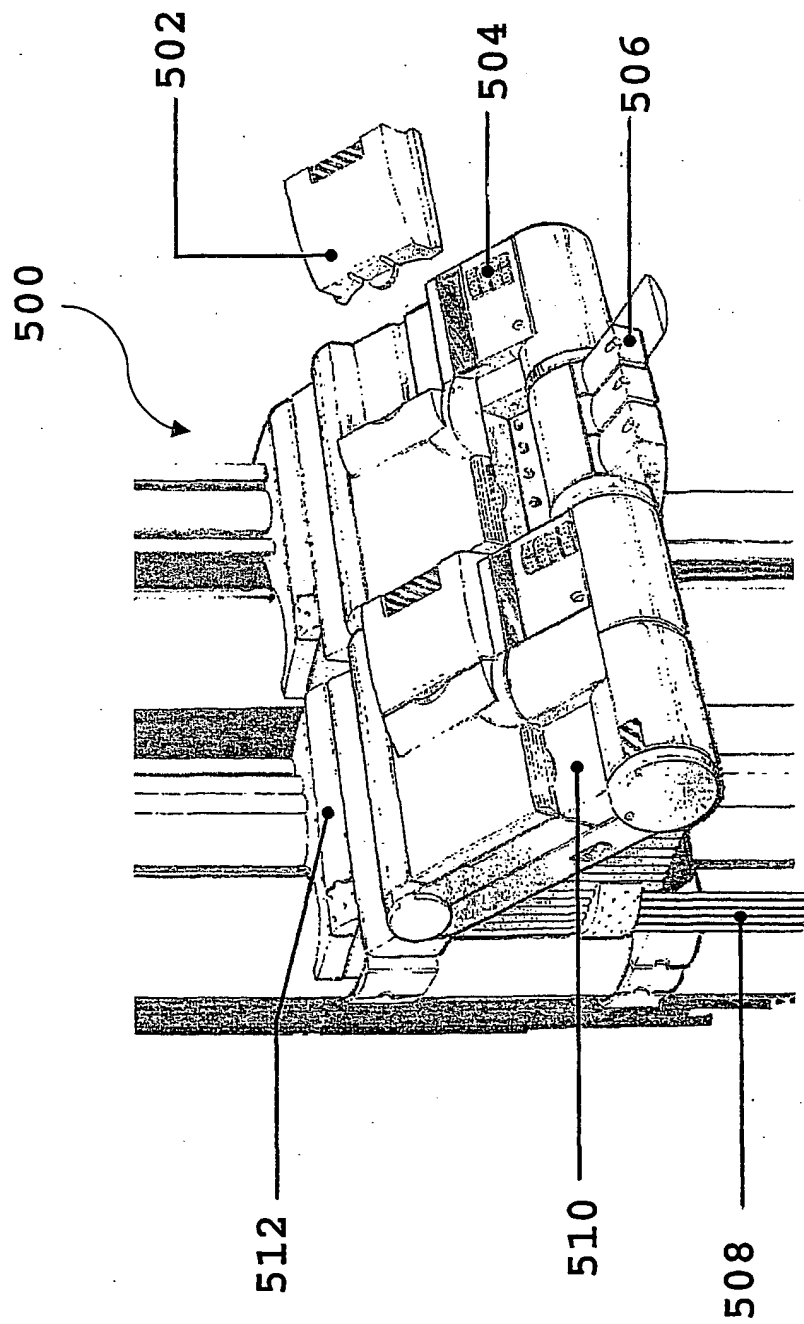


Fig. 12

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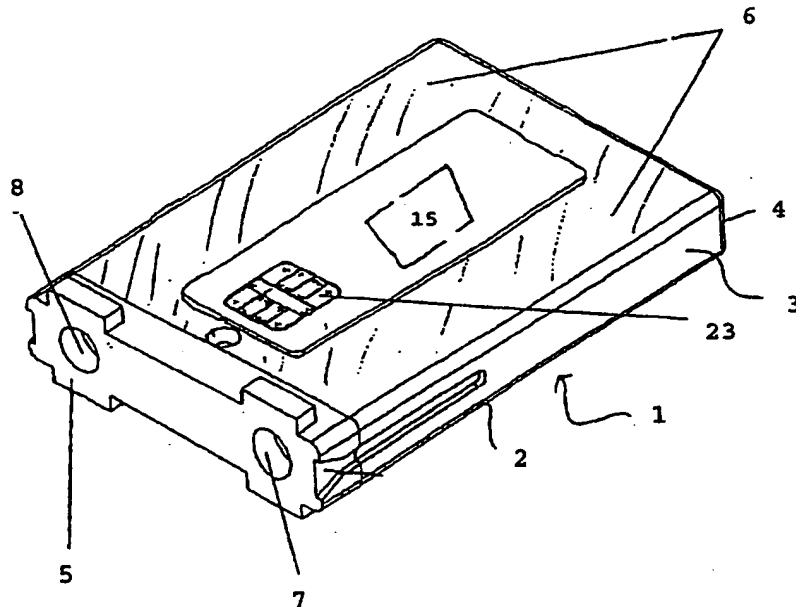
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[Continued on next page]

(54) Title: FLUID SEPARATION CONDUIT CARTRIDGE



(57) Abstract: A fluid separation conduit cartridge comprising a fluid separation conduit is disclosed. In certain embodiments the fluid separation conduit is potted to provide operation at increased pressures. In other embodiments, the fluid separation conduit cartridge has one or more memory units. The memory units are operative to store data such as, for example, cartridge usage and test results.

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INTERNATIONAL SEARCH REPORT

International Application No

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 295 22 076 U (HEWLETT PACKARD GMBH) 2 September 1999 (1999-09-02) page 1, line 5-10 page 2, line 23 -page 3, line 10 page 4, line 5 -page 5, line 25 page 7, line 7 -page 8, line 20 ---	1,23
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A	US 4 586 733 A (ANDERSON JR JAMES M) 6 May 1986 (1986-05-06) column 2, line 50 -column 3, line 64; figures 1,2 --- -/--	1,10,20, 23

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 512 899 A (GOODNIGHT JR LYMAN E) 23 April 1985 (1985-04-23) abstract; figure 2 ---	1,10,20, 23
A	US 5 744 100 A (KRSTANOVIC SRDJAN) 28 April 1998 (1998-04-28) column 4, line 21-63; figure 1B ---	1,10,20, 23
X	EP 0 636 882 A (MICROSENSOR TECHNOLOGY INC) 1 February 1995 (1995-02-01) ---	20,21
A	column 2, line 50 -column 5; figures 1,3,7 -----	1,10,23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/31291

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-15, 20, 21, 23-28

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15,20,21,23-28

Conduit end fittings

2. Claims: 16-19,22

Potting the conduit in the housing

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/31291

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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